

(a) A single species from the peptide hormone superfamily, comprising (1) PACAP, (2) PACAP-like peptide, (3) VIP, (4) Glucagons, (5) Glucagon-like peptides, (6) Secretin, (7) Helodermin, and (8) Exendin-4 (relevant to at least claims 2, 39 and 55);

(b) A single species of peptide, comprising (1) adrenocorticotrophic hormone, (2) angiotensins, (3) rennin substrate, (4) tetradecapeptide, (5) natriuretic peptides, (6) gastrointestinal peptides, (7) luteinizing hormone releasing hormone, (8) melanocyte stimulating hormone, (9) neurotensin, and (10) parathyroid hormone (relevant to at least claims 5, 41 and 57);

(c) A single species of transition metal salt, comprising (1) zinc, (2) copper, (3) iron, (4) manganese, (5) nickel, and (6) cobalt (relevant to at least claims 6, 7, 24, 32, 42, 43, 52 and 58);

(d) A single species of organic solvent, comprising (1) DMSO, (2) 1-methyl-2-pyrrolidinone, (3) propanol, (4) propylene glycol, (5) glycerol acetate, (6) monothioglycerol, (7) acetic acid, (8) diethanolamine, (9) benzyl alcohol, (10) ethyl lactate, (11) glycerol formal, (12) N-methylpyrrolidone, (13) polyethyleneglycol 400, and (14) isopropyl myristate (relevant to at least claims 8-10, 12-14, 36-38, and 61-63);

(e) A single species of dried mixture, comprising (1) acid and (2) peptide (relevant only to claim 17); and

(f) A single species of inorganic acid, comprising (1) HCl and (2) H₃PO₄ (relevant to at least claims 20, 29 and 46).

In response to the election requirement, applicants provisionally elect, with traverse, the following:

- (a) Peptide hormone superfamily: PACAP;
- (b) Peptide: adrenocorticotrophic hormone;
- (c) Salt of transition metal: zinc;
- (d) Organic solvent: DMSO;
- (e) Dried mixture: acid; and
- (f) Inorganic acid: HCl.

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The examiner has failed to understand the presently-claimed invention, has completely mischaracterized the species of the invention, and has failed to follow the rules for determining unity of invention. Accordingly, the election requirement and the determination of lack of unity of invention are deemed to be improper. Reconsideration and withdrawal of both are requested.

OUTLINE OF THE LAW CONCERNING UNITY OF INVENTION:

MPEP §1893.03(d): Unity of Invention

Unity of invention (not restriction) practice is applicable in international applications (both chapter I and chapter II) and in national stage applications submitted under 35 U.S.C. §371 (MPEP 1893.03(d)).

When making a lack of unity of invention requirement, the examiner must (1) list the different groups of claims and (2) explain why each group lacks unity with each other group (i.e., why there is not single general inventive concept) specifically describing the unique special technical feature in each group (MPEP 1893.03(d)).

The application of unity of invention considerations is set forth in MPEP §1850.

MPEP §1850: Unity of invention Before the International Searching Authority

PCT Rule 13.1

The international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity if invention").

PCT Rule 13.2

Where a group of inventions is claimed in one and the same international application, the requirement of unity if invention referred to in Rule 13.1 shall be fulfilled only when there is a

technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

PCT Rule 13.3

The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

PCT Rule 13.4

Subject to Rule 13.1, it shall be permitted to include in the same international application a reasonable number of dependent claims, claiming specific forms of the invention claimed in an independent claim, even where the features of any dependent claim could be considered as constituting in themselves an invention.

Any international application must relate to one invention only or to a group of inventions so linked as to form a single general inventive concept (PCT Article 3(4)(iii) and 17(3)(a), PCT Rule 13.1, and 37 CFR 1.475. (MPEP 1850)

When the Office considers international applications as an International Searching Authority, as an International Preliminary Examining Authority, and during the national stage as a Designated or Elected Office under 35 U.S.C 371, PCT Rule 13.1 and 13.2 will be followed when considering unity of invention of claims of different categories without regard to the practice in national applications filed under 35 U.S.C. 111. (MPEP 1850)

In applying PCT Rule 13.2 to international applications and to national stage applications under 35 U.S.C. 371, examiners should consider for unity of invention all the claims to different categories of invention in the application and permit retention in the same application

for searching and/or preliminary examination, claims to the categories which meet the requirements of PCT Rule 13.2. (MPEP 1850)

PCT Rule 13.2, as it was modified effective July 1, 1992, no longer specifies the combinations of categories of invention which are considered to have unity of invention. Those categories, which now appear as a part of Chapter 10 of the International Search and Preliminary Examination Guidelines, may be obtained from WIPO's website (www.wipo.int/pct/en/texts/gdlines.htm). (MPEP 1850)

Chapter 10 of the International Search and Preliminary Examination Guidelines also contains examples concerning unity of invention. (MPEP 1850)

An international application should relate to only one invention or, if there is more than one invention, the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept (PCT Rule 13.1). With respect to a group of inventions claimed in a international application, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" is defined in PCT Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description and drawings (if any). (MPEP 1850)

Whether or not any particular technical feature makes a "contribution" over the prior art, and therefore constitutes a "special technical feature" should be considered with respect to novelty and inventive step. (MPEP 1850)

Lack of unity of invention may be directly evident "*a priori*", that is, before considering the claims in relation to any prior art, or may only become apparent "*a posteriori*", that is, after

taking the prior art into consideration. For example, independent claims to A+X, A+Y, and X+Y can be said to lack unity of invention *a priori* as there is no subject matter common to all claims. In the case of independent claims to A+X and A+Y, unity of invention is present *a priori* as A is common to both claims. However, if it can be established that A is known, there is lack of unity *a posteriori*, since A (be it a single feature or a group of features) is not a technical feature that defines a contribution of the prior art. (MPEP 1850)

Although lack of unity of invention should certainly be raised in clear cases, it should neither be raised nor maintained on the basis of a narrow, literal or academic approach. There should be a broad, practical consideration of the degree of interdependence of the alternatives presented, in relation to the state of the art as revealed by the international search or in accordance with PCT Article 33(6), by any additional document considered to be relevant. If the common matter of the independent claims is well known and the remaining subject matter of each claim differs from that of the others without there being any unifying novel inventive concept common to all, then clearly there is lack of unity of invention. If, on the other hand, there is a single general inventive concept that appears novel and involves inventive step, then there is unity of invention and an objection of lack of unity does not arise. For determining the action to be taken by the examiner between these two extremes, rigid rules cannot be given and each case should be considered on its merits, the benefit of any doubt being given to the applicant. (MPEP 1850)

....the International Searching Authority or the International Preliminary Examining Authority should not raise objection of lack of unity of invention merely because the inventions claimed are classified in separate classification groups or merely for the purpose of restricting the international search to certain classification groups. (MPEP 1850)

Unity of invention has to be considered in the first place only in relation to the independent claims in an international application and not the dependent claims. By "dependent" claim is meant a claim which contains all the raptures of one or more other claims and contains a

reference, preferably at the beginning, to the other claim or claims and then states the additional features claimed (PCT rule 6.4). The examiner should also bear in mind that a claim may also contain a reference to another claim even if it is not a dependent claim as defined in PCT Rule 6.4. One example of this is a claim referring to a claim of a different category (for example, "Apparatus for carrying out the process of Claim 1.....", or "Process for the manufacture of the product of Claim 1....."). Similarly, a claim to one part referring to another cooperating part, for example, "plug for cooperation with the socket of Claim 1 ..." is not a dependent claim. (MPEP 1850)

If the independent claims avoid the prior art and satisfy the requirement of unity of invention, no problem of lack of unity arises in respect of any claims that depend on the independent claims. In particular, it does not matter if a dependent claim itself contains a further invention. (MPEP 1850)

If, however, an independent claim does not avoid the prior art, then the question whether there is still an inventive link between all the claims dependent on that claim needs to be carefully considered. If there is no link remaining, an objection of lack of unity *a posteriori* (that is, arising only after assessment of the prior art) may be raised. Similar considerations apply in the case of a genus/species or combination/subcombination situation. (MPEP 1850)

Objection of lack of unity of invention does not normally arise if the combination of a number of individual elements is claimed in a single claim even if these elements seem unrelated when considered individually. (MPEP 1850)

Unity of Invention in Markush practice

An international application must relate to one invention only, or, if there is more than one invention, those inventions must be linked so as to form a single general inventive concept (Rule 13.1). Inventions are considered linked so as to form a single general inventive concept only when there is a technical relationship involving one or more of the same or corresponding

special technical features. The expression "special technical features" means those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art (Rule 13.2).

Annex B of the PCT Administrative Instructions explains the method for determining unity of invention contained in Rule 13.2 in greater detail with respect to three particular situations: (i) combinations of different categories of claims, (ii) Markush practice, and (iii) intermediate and final products (Annex B, Part 1(d)).

Markush practice under Rule 13.2 is dealt with in the PCT Administrative Instructions, Annex B, Part 1(f). In "Markush practice", a single claim defines alternatives, chemical or non-chemical. The requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2 are considered to be met when the alternatives are of a similar nature.

According to Annex B, Part 1(f)(i), when the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:

- (A) all alternatives have a common property or activity, and
- (B)(1) a common structure is present, i.e., a significant structural element is shared by all of the alternatives, or
- (B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

Annex B, Part 1(f)(ii): In paragraph (f)(i)(B)(1), above, the words "significant structural element is shared by all of the alternatives" refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art. The structural element may be a single component or a combination of individual components linked together.

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Annex B, Part 1(f)(iii): In paragraph (f)(i)(B)(2), above, the words “recognized class of chemical compounds” mean that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other, with the expectation that the same intended result would be achieved.

Appendix B, part 2, provides examples concerning unity of invention. Part I relates to claims in different categories. Part II relates to claims in the same category. Part III relates to Markush practice. The examples provided in part III (Markush practice) show that the common structure shared by all of the alternatives does not need to be a patentable advance over the art, so long as it occupies a large portion of the structures of the alternatives, in accordance with Annex B, part 1(f)(ii). As indicated in Annex B, part 1(f)(ii), it is only in case the compounds have in common only a small portion of their structures that the commonly shared structure should constitute a structurally distinctive portion in view of the existing prior art. Note, moreover, that the foregoing language does not state that the common structural feature must be a patentable advance over the prior art. It may possibly mean only that the commonly shared structure should be “distinctive” in the sense that this structural feature has not previously been employed in the context of similar compounds of the prior art.

DISCUSSION OF THE PRESENT INVENTION

The invention relates to “novel methods of controlling peptide instability in organic solvents, in organic-based suspensions, and in dried state” and provides stabilized peptide formulations “that are stabilized by a transition metal salt, an acid or both.” See Paragraph 6 of the published application, U.S. 2005/0009739. Accordingly, the present invention relates to stabilized peptide formulations, either in solution, a suspension, or as a dried mixture, and processes for preparing same. These peptide formulations and processes for preparing same are defined in the independent claims and further elaborated in the dependent claims.

The independent claims of the present application, which under the rules are properly the basis for a determination of unity of invention, are as follows:

1. A stabilized peptide formulation, either in a solution or in a suspension, comprising:
 - (a) a peptide containing at least one histidine residue;
 - (b) a transition metal salt; and
 - (c) a pharmaceutically acceptable organic solvent.
11. A stabilized peptide formulation, either in a solution or in a suspension, comprising:
 - (a) PACAP 66 (SEQ ID NO: 1) and/or salts thereof;
 - (b) $ZnCl_2$; and
 - (c) a pharmaceutically acceptable organic solvent.
17. A stabilized peptide formulation, comprising a dried mixture of an acid and a peptide containing at least one asparagine residue.
26. A stabilized peptide formulation, comprising a dried mixture of an acid and PACAP 66 (SEQ ID NO: 1) and/or a salt thereof.
34. A stabilized peptide formulation, comprising a dried mixture of a transition metal salt and a peptide containing at least one histidine residue.
44. A process for preparing a stabilized peptide formulation, comprising the steps of:
 - (a) preparing an acid solution of acid and water;
 - (b) cooling said acid solution to below room temperature;
 - (c) mixing said cooled acid solution and a peptide containing at least one asparagine residue to create a cooled mixture; and
 - (d) drying said cooled mixture.
54. A process for preparing a stabilized peptide formulation, comprising the steps of:
 - (a) mixing an aqueous solution containing a transition metal salt with a peptide containing at least one histidine residue; and
 - (b) drying said mixture.

From this claims listing, it is clear that claims 1, 2, 17, 26, and 34 relate to stabilized peptide formulations. Claims 1 and 11 recite formulations in either a solution or a suspension. Claims 17, 26, and 34 recite stabilized formulations in the form of dried mixtures. From the above claims listing, it is also clear that claims 44 and 54 relate to processes for preparing the stabilized peptide formulations in the dried form. It is these independent claims which the examiner should have considered in making her determination whether unity of invention is present or not.

The dependent claims of the application provide further definitions of the various elements of the independent claims. The particular materials listed in the dependent claims are not species of the invention as the examiner mistakenly states.

In section 1 of the Office action, the examiner states that the applicant is required to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable, and that the reply must also identify the claims readable on the elected species. It is impossible to comply with these requirements, as the species identified by the examiner are not species of the invention.

Also in section 1 of the Office action, the examiner states that "all disclosed variables must be elected to a single disclosed species", and provides a further explanation of what is meant by this. In response, the applicants have identified one material from each of the identified variables, and these are listed above.

In section 2 of the Office action, the examiner states that "the claims are deemed to correspond to the species listed above in the following manner: Claims 2, 5, 6, 8-10, 12-14, 17, 20-21, 24, 29, 32, 36-39, 41, 42, 46, 52, 55, 57, 58, 61, 62, and 63." So far as the applicants can discern, this listing is merely a list of claims in which elements of the other claims are further elaborated, except for claim 17. Claim 17 is an independent claim which recites a stabilized peptide formulation comprising a dried mixture of an acid and a peptide containing at least one

asparagines residue. Its inclusion in the examiner's list of "species" is the only species of the invention which the examiner has correctly identified, but the elements of this claim are not species of the invention.

In section 3 of the Office action, the examiner states that "the species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding technical features", and then proceeds to discuss why they are different. The examiner is correct that the species she has identified do not relate to a single general inventive concept; the reason is that the identified "species" are not species of the invention at all, as discussed above. Accordingly, the examiner's conclusion of lack of unity of invention is wholly without merit.

The rules require the following, among other things:

1. Application of the PCT unity of invention standards in national stage applications under §371. The examiner has purported to do this, but has not followed the rules.
2. Consideration of unity of invention in the first place only in relation to the independent claims in an international application, and not the dependent claims. The examiner has not done this. She has instead focused on the dependent claims and has improperly defined the materials listed in these dependent claims as "species" of the invention.
3. Providing a listing of the different groups of claims and an explanation why each group lacks unity with each other group. The examiner has not done this.
4. Consideration for unity of invention all the claims to different categories of invention in the application. The examiner has not done this.
5. Not raising or maintaining lack of unity of invention on the basis of a narrow, literal, of academic approach. The examiner has not followed this directive.
6. A practical evaluation whether there is a general inventive concept reflected in the independent claims. The examiner has failed to provide this.
7. Not raising an objection of lack of unity of invention merely because the inventions claimed are classified in separate classification groups or merely for the purpose of

restricting the application search to certain classification groups. The examiner appears to be attempting to split the application for the purpose of minimizing the search requirements to a minimum number of classification groups.

8. Consideration of the claims to determine whether any of them constitute the combination of a number of individual elements, for which the MPEP materials state objection of a lack of unity of invention does not normally arise. The examiner has failed to recognize that each of the formulation claims (1, 11, 17, 26, and 34) recites a combination of individual elements (though broadly stated).

In view of the foregoing remarks, it is deemed that the election requirement is improper and should be withdrawn, and a proper evaluation of whether unity of invention is or is not present in the claims of this application should be carried out under the applicable rules. Such a reconsideration and re-determination are accordingly requested.

Respectfully submitted,

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